UNITED STATES PATENT AND TRADEMARK OFFICE

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10/789,424	02/27/2004	Srinivasa Nagalla	PTX-0003	5692

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EXAMINER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.
- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
  Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *03 June 2009 and 14 May 2009*.
2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-84* is/are pending in the application.
    4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) *1-84* is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.
10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
    Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
    Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
    a) ☐ All b) ☐ Some * c) ☐ None of:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____.
      3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
    * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
    Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
    Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Applicants response filed 06/03/2009 is acknowledged.

Claims 1-84 are pending and are currently under examination. Claims 85-90 are cancelled.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-84 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The recent en banc decision regarding Bilski v. Warsaw (2008) set forth that a process is patent-eligible if (1) it is ties to a particular machine or apparatus or (2) it transforms a particular article into a different state or thing. Further, the recent decision in Comiskey (2009) confirmed the opinion set forth in Bilski of the prohibition pre-empting an abstract idea or mental process in a claim. The revised Comiskey decision further reiterated the president set forth in Richman, 563 F.2d 1026, 1030 (CCPA 1977)

wherein the court held the application unpatentable because "if a claim [as a whole] is directed essentially to a method of calculating, using a mathematical formula, even if the solution is for a specific purpose, the claimed method is nonstatutory."

The claimed process comprises the abstract/computational steps of calculating at least one mass-based alignment, interpreting mass differences of modification sites, and calculating at least one match score, and storing said score on a computer readable medium. In the instant case, the ultimate step of storing a score on computer readable media is considered an inconsequential post solution activity. The instant claims do not recite or inherently involve any transformation of an article, therefore the Examiner must determine if the instant claims have a tie to a particular machine or apparatus. Instant claims 1-84 do not recite any limitation that ties the recited abstract process to any particular machine or apparatus. It is further noted that the instant claims have been amended to further recite 'providing data... to a computer-based system" (see for example independent claim 1). However, the limitation of a "computer-based system" does not provide any meaningful limits to the instant claims as to what, if any, particular machine or apparatus is encompassed thereby or required for practicing the recited process. Further, upon review, the specification does not provide any definition for the recited term "computer-based system". Therefore, it is maintained that the instant claims are directed to non-statutory subject matter as they wholly preempt the abstract process as set forth above.

Response to Arguments

Applicant's arguments filed 06/03/2009 have been fully considered but they are

not persuasive.

In regards to the rejection of claims under 35 USC §101 as being directed to non-

statutory subject matter, applicants argue that the claims are believed to be statutory in

view of claim amendments directed to a computer-based system.

In response, applicants argument is not persuasive because said amendments

are insufficient to either (1) tie the instant claims to a particular machine or apparatus or

otherwise (2) transform a particular article into a different state or thing.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all

obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set
> forth in section 102 of this title, if the differences between the subject matter sought to be patented and
> the prior art are such that the subject matter as a whole would have been obvious at the time the
> invention was made to a person having ordinary skill in the art to which said subject matter pertains.
> Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of

the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g)

prior art under 35 U.S.C. 103(a).

Claims 1-12 and 63-84 are rejected under 35 U.S.C. 103(a) as being

unpatentable over Dancik et al. (J. Comp. Biol., 1999) in view of Pevzner et al. (see IDS

filed 02/11/2005). The rejection of claims 81 are necessitated by amendments made to

the instant claims.

The instant claims are drawn to a method for identifying a macromolecule having

a sequence and sequence modification thereof from mass spectrometry data

comprising providing at least one de novo sequence from mass spectroscopy data,

calculating at least one mass-based alignment between each de novo sequence and a

sequence in a sequence database, comparing molecular masses of fragments to

molecular masses of sequence fragments contained in a sequence database,

interpreting mass differences of modification sites between sequences in said database

and at least one de novo sequence using a modification catalog, and calculating at least

one match score for the mass-based alignment. Further claimed embodiments of the

method comprises the additional steps of identifying sequences in the sequence

database from mass-based alignments in response to the match score, and grouping

identification of sequences from at least one de novo sequence into an identified

macromolecule list that agrees with the mass.

It is first noted that the amendment to the instant claims "wherein said

modification contains information for accurately identifying sequence variations and

post-translational protein modifications" comprises nothing more than recitation of non-

functional descriptive, per se. Non-functional descriptive material, per se, is not afforded

patentable weight when differentiating the instant claims from that which is taught in the

prior art. See Ex parte Nehls (2008) and Ex parte Puglisi (2009).

      Dancik et al. sets forth a review of de novo peptide and protein sequencing

techniques via tandem mass spectrometry and the development of a software

algorithm, SHERENGA (see Dancik et al., Abstract). Dancik et al. further sets forth that

SHERENGA addresses an art recognized need for the previously unsolved computation

problems drawn to parameter learning, spectrum graphing, scoring schema, and

sequencing algorithms (see Dancik et al., page 328, lines 24-45). Dancik et al. discloses

methods for the identification of peptide and protein sequences using a tandem mass

spectrometer capable of ionizing a mixture of peptides with different sequences and

measuring their respective parent mass/charge ratios, selectively fragmenting each

peptide into pieces and measuring the mass/charge ratios of the fragment ions (MS/MS

spectra) and interpreting such MS/MS relies upon a data base searching (see Dancik et

al., page 327, lines 1-11). Dancik et al. discloses that the automated SHERENGA

further provides for improved *de novo* interpretation that automatically learns fragment

ion types and intensity thresholds from a collection of test spectra generated from any

type of mass spectrometer, wherein test data is used to construct optimal path scoring

in the graph representations of MS/MS spectra and a ranked list of high scoring paths

corresponding to potential sequences (see Dancik et al., Abstract and page 329, lines

1-27; page 330, lines 1 through page 333, line 9; and page 333, line 39 through page

336, line 5). Dancik et al. further disclose that peptides were obtained from in-gel or in-

solution tryptic digestion of proteins isolated from yeast lysates, mouse plasma, and

urine (see Dancik et al., page 338, lines 1-4). Dancik et al. further disclose an

automated approach for scoring how well a candidate sequence "explains" a spectrum

and then and selecting sequences that provide a best fit to a given spectrum. The

disclosed scoring method relies upon an evaluation of probability that a given sequence

P produces a given spectrum S via maximizing a probability function p(P,S) (see Dancik

et al., page 334, line 19 through page 336, line 5). Dancik et al. further provides results

by the disclosed methods in Figures 5-9 (see Dancik et al. page 336, line 34 through

page 337, line 20). Examples of interpretation with different quality are reflected by

ambiguities in initial and/or terminal 1-3 amino acids (see page 336, line 34 through

page 337, line 5). Dancik et al. further displays and labels mass objects relied upon to

reflect different qualities of interpretation in Figure 10. To evaluate the performance of

the disclosed de novo algorithms, Dancik et al. introduces the use of ladder difference

metric between the predicted and actual sequences (see Dancik et al., page 337, lines

6-20).

While Dancik et al. sets forth the above discussed approaches to identifying

sequences of molecules from mass spectrometry data, Dancik et al. does not fairly

teach or suggest interpreting mass differences of modification between a sequence in a

database and a de novo sequences that has been identified by mass based alignment

as modifications in a modification catalog (see for example step (c) of instant claim 1).

Pevzner et al. sets forth methods drawn to efficient database searching for

identification of mutated and modified proteins via mass spectrometry. Pevzner et al.

further teach that the disclosed methods and algorithms address an art recognized need

for algorithms that sort out reliable database hits from unreliable ones and identify

mutated and modified peptides (see Pevzner et al., Abstract). Pevzner et al. further set

forth that the disclosed approaches demonstrate advantages over known prior art

methods and further demonstrate the use of a spectral alignment approach as a filter in

a new database search algorithm that reliably identifies peptides differing by up to two

mutations/modifications from a peptide in a database (see Pevzner et al., Abstract).

Figure 1 and Table 1 of Pevzner et al. list a plurality modified peptides used in the

disclosed methods read on a modification catalog as instantly claimed. Further, Pevzner

et al. rely upon MS/MS sequence methods to identify by mass based alignment to

correlate sequence fragments to the modified peptides set forth in Figure 1 and Table 1

(see Pevzner et al., page 295, col. 2, line 43 through page 299, col. 1, line 15). Pevzner

et al. further sets forth the application of spectral convolution of experimental and

theoretical spectra that allow for the detection of mutations/modification without an

exhaustive search (see Pevzner et al., page 292, col. 2, line 35 through page 294, col.

2, line 30). Figure 2 of Pevzner et al. further demonstrates the use of a set of

differences matrixes, which are fairly interpreted as substitution matrixes, required to

practice the spectral convolution procedures.

Therefore it would have been obvious at the time the invention was made to a

person having ordinary skill in the art to which said subject matter pertains to use the

disclosed methods for the identification of sequences using a tandem mass

spectrometry, as set forth by Dancik et al., in combination with the methods drawn to

efficient database searching for identification of mutated and modified proteins via mass spectrometry, as set forth by Pevzner et al. One of skill in the art would be motivated to combine the teachings of Dancik et al. and Pevzner et al. because Pevzner et al. teaches that the disclosed methods and algorithms address an art recognized need for algorithms that sort out reliable database hits from unreliable ones and identify mutated and modified peptides. One of ordinary skill in the art would further recognize that the combination of Dancik et al. and Pevzner et al. would yield expected results.

Claims 1-27 and 63-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dancik et al. in view of Pevzner et al., as applied to claims 1-12 and 63-84 above, and further in view of Mann et al. (see IDS filed 02/11/2005). The rejection of claim 81 is necessitated by amendments made to the instant claims.

The instant claims recite further embodiments comprising the steps of identifying a sequence in the sequence database with a tag match and generating a mass-based alignment between a de novo sequence and a sequence in the sequence database.

Dancik et al. in view Pevzner et al. provide for the above discussed methods of identifying sequences using a tandem mass spectrometry, as set forth by Dancik et al., in combination with the methods drawn to efficient database searching for identification of mutated and modified proteins via mass spectrometry, as set forth by Pevzner et al. However, neither Dancik et al. nor Pevzner et al. fairly teach or suggest identifying a sequence in a sequence database with a tag match (see for example, step (a) of instant claim 13).

Mann et al. demonstrate an approach to the identification of mass

spectrometrically fragmented peptides (see Mann et al., Abstract). Mann et al. set forth

that the disclosed methods as a means for interpreting complex tandem mass spectra

by use of searching by peptide sequence tags (see Mann et al., page 4390, col. 2, lines

1-32). Mann et al. further demonstrate that MS/MS data can be relied upon for peptide

identification with tags as short as two amino acids that can further be located in the

presence of posttranscriptional modification or a sequence difference between the

measured peptide and the peptide database (see especially Mann et al., page 4390,

col. 2, lines 23-31 and page 4393, col. 1, line 25 through page 4397, col. 2, line 3).

Therefore it would have been obvious at the time the invention was made to a

person having ordinary skill in the art to which said subject matter pertains to use the

disclosed methods for the identification of sequences using a tandem mass

spectrometry, as set forth by Dancik et al., in combination with the methods drawn to

efficient database searching for identification of mutated and modified proteins via mass

spectrometry, as set forth by Pevzner et al., and in further combination with searching

methods that rely on peptide sequence tags, as set forth by Mann et al. One of skill in

the art would be motivated to combine the teachings of Dencik et al., Pevzner et al., and

Mann et al., because Mann et al. teaches that the error tolerance of the peptide

sequence tag approach is very high and is crucial in cases where predicted mass

peptides is likely to be wrong (see especially, Mann et al., page 4398, col. 1, lines 22-

37). One of ordinary skill in the art would further recognize that the combination of

Dancik et al., Pevzner et al., and Mann et al. would yield expected results.

Claims 1-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over

Dancik et al. in view of Pevzner et al. in view of Mann et al. as applied to claims 1-27

and 63-84 above, and further in view of Bader (Bioinformatics, 2003). The rejection of

claim 81 necessitated by amendments made to the instant claims.

The instant claims recite further embodiments comprising generating mass-

based alignment using a breadth-first search (see for example instant claim 28).

Dancik et al. in view Pevzner et al. in view of Mann et al. provide for the above

discussed methods of identifying sequences using a tandem mass spectrometry, as set

forth by Dancik et al., in combination with the methods drawn to efficient database

searching for identification of mutated and modified proteins via mass spectrometry, as

set forth by Pevzner et al., and in further combination with searching methods that rely

on peptide sequence tags, as set forth by Mann et al. However, neither Dancik et al.,

Pevzner et al., nor Mann et al. fairly teach or suggest generating mass-based alignment

using a breadth-first search.

Bader sets forth methods related to extracting relevant complexes and pathways

from high-throughput proteomics data sets to identify and extract networks are that

essential to the art recognized problem of building pathways starting from known

proteins of interest (see Bader, page 1869, col. 1, lines 1-10). Bader discloses the

developed of an efficient algorithm, SEEDY, that extracts biologically relevant biological

networks from protein–protein interaction data, building out from selected seed proteins.

The algorithm relies on a previous study establishing statistical confidence levels for

interactions generated by two-hybrid screens and inferred from mass spectrometric

identification of protein complexes (see Bader, page 1869, col. 1, lines 11-25). Bader

further discloses the evaluation of the disclosed algorithm by use of a breadth-first

outward search based on an outward traversal of a protein interaction network (see

Bader, page 1870, col. 2, lines 5-22).

Therefore it would have been obvious at the time the invention was made to a

person having ordinary skill in the art to which said subject matter pertains to use the

disclosed methods for the identification of sequences using a tandem mass

spectrometry, as set forth by Dancik et al., in combination with the methods drawn to

efficient database searching for identification of mutated and modified proteins via mass

spectrometry, as set forth by Pevzner et al., in combination with searching methods that

rely on peptide sequence tags, as set forth by Mann et al., and in further combination

with the use of a breadth-first outward search based on an outward traversal of a

protein interaction network, as set forth by Bader. One of skill in the art would be

motivated to combine the teachings of Dencik et al., Pevzner et al., and Mann et al.,

because Bader teaches that the disclosed breadth-first outward search is applicable to

the analysis of an algorithms inferred from mass spectrometric identification of protein

complexes. One of ordinary skill in the art would further recognize that the combination

of Dancik et al., Pevzner et al., Mann et al. and Bader et al. would yield expected

results.

Response to Arguments

Applicant's arguments filed 06/03/2009 have been fully considered but they are not persuasive.

In regards to the rejection of claims under 35 U.S.C. 103(a) as being unpatentable over Dancik et al. in view of Pevzner et al., applicants reiterate previous presented arguments directed toward the prior art of record in comparison to *the exact terms recited in the instant claims*. As such, applicants arguments are not persuasive for reasons already of record.

It is emphasized that the recent Supreme Court decision in KSR Intl. Co. v. Teleflex Inc. rejected the rigid approach of applying a strict TSM test as the sole basis for obviousness and that the analysis *for obviousness need not seek out precise teachings directed to the specific subject matter of a claim*. Further the decision set forth that *the analysis can take into account the inferences and creative steps that a person of ordinary skill in the art could employ and that a person of ordinary skill in the art is also a person of ordinary creativity*, not an automaton. Further, the decision set forth that a combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.

Applicants reiterated arguments only serve to emphasize where the precise language of the instant claims is not found in the prior art relied upon in the instant rejection. It is emphasized that the instant rejection is not based upon a finding of exact anticipation as would be required under 35 USC § 102, but is rather based upon a finding of obviousness under 35 USC 103(a). The examiner acknowledges that, as set

forth in the rejection above, there are differences between the precise teachings of the art and the precise limitations recited in the instant claims. However, upon full consideration and review of the art of record, these differences all appear to be well within the scope of the skill set attributed to an artisan in this field. Applicants reiterated arguments do not establish how any of the differences rise above a mere more combination of familiar elements which yield predictable results as seen through the eyes of one of skill in this art.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERIC S. DEJONG whose telephone number is (571)272-6099. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Marjorie Moran can be reached on (571) 272-0720. The fax phone number

for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the

Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information

system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ERIC S. DEJONG/
Primary Examiner, Art Unit 1631